PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:

STEPHEN M. ALLEN ET AL.

CASE NO: BB1157 US CNT

SERIAL NO: 10/659,199

GROUP ART UNIT: 1638

FILED: SEPTEMBER 10, 2003

EXAMINER: KUBELIK, ANNE R.

FOR: A NUCLEIC ACID ENCODING A WHEAT BRITTLE-1 HOMOLOG

APPEAL BRIEF

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Sir:

Pursuant to 37 C.F.R. § 1.192, the following is an Appeal Brief submitted in response to the Notification of Non-Compliant Appeal Brief mailed January 30, 2008.

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I. REAL PARTY IN INTEREST

The real party in interest is E.I. du Pont de Nemours and Company (*hereinafter* "DuPont"), owner of the Application.

II. RELATED APPEALS AND INTERFERENCES

There are no other appeals or interferences known to Applicants, Applicants' legal representative, or DuPont that will directly affect or be directly affected by or have a bearing on the Board of Patent Appeals and Interferences' (*hereinafter* the "Board") decision in the present Appeal.

III. STATUS OF THE CLAIMS

Claims 26-29 stand rejected and are the subject of this Appeal. Originally-filed Claims 1-25 have been canceled.

IV. STATUS OF AMENDMENTS

No amendments were made to the claims in response to the Final Office Action.

V. SUMMARY OF CLAIMED SUBJECT MATTER

Claim 26, the only independent claim at issue, relates to an isolated polynucleotide comprising: (a) a nucleotide sequence encoding a polypeptide having brittle-1 activity (*see, e.g.*, Applicants' Specification at page 6, lines 17-21), wherein the polypeptide has an amino acid sequence of at least 90% sequence identity when compared to SEQ ID NO:18 (*see, e.g.,* Applicants' Specification at page 8, line 34 – page 9, line 17; page 14, lines 16-36), or (b) a full-length complement of the nucleotide sequence of (a) (*see, e.g.,* Applicants' Specification at page 8, lines 19-33; page 12, lines 3-7).

VI. GROUNDS OF REJECTION TO BE REVIEWED ON APPEAL

Whether claims 26-29 are supported by sufficient written description under 35 U.S.C. § 112, 1st Paragraph.

Whether claims 26-29 are enabled under 35 U.S.C. § 112, 1st Paragraph.

VII. ARGUMENT

A. Claims 26-29 Comply with the Written Description Requirement of 35 U.S.C. § 112, 1st Paragraph.

Claims 26-29 stand rejected under 35 USC 112, first paragraph, as failing to comply with the written description requirement. During the course of prosecution, the Examiner asserted that "the specification only describes a coding sequence from wheat that comprises SEQ ID NO:17. Applicant does not describe other nucleic acids encompassed by the claims, and the structural and functional features that distinguish all such nucleic acids from other nucleic acids are not provided." June 20, 2005, Non-Final Office Action, at 6 (*hereinafter* "Non-Final OA"). The Examiner further asserted that "[n]o description is provided as to the function of the encoded protein." *Id.*; *see also* March 8, 2006, Final Office Action, at 8 (*hereinafter* "First Final OA"). The Examiner thus concluded that "Applicant has not, in fact, described nucleic acids that encode a protein with 90% identity to SEQ ID NO:18 within the full scope of the claims, and the specification fails to provide an adequate written description of the claimed invention." Non-Final OA, at 6; *see also* First Final OA, at 9.

Applicants' claimed invention, however, substantially conforms to Example 14 of the "Synopsis of Application of Written Description Guidelines", 66 Fed. Reg. 1099 (Jan. 5, 2001), *available at* http://www.uspto.gov/web/menu/written.pdf (last visited Oct. 5, 2007) (*hereinafter* "Written Description Guidelines"). In Example 14, the exemplary claim is directed to "A protein having SEQ ID NO:3 and variants thereof that are at least 95% identical to SEQ ID NO:3 and catalyze the reaction of A→B." Written Description Guidelines, at 53. Included in the Example 14 specification is an "indicat[ions] that procedures for making proteins with substitutions, deletions, insertions and additions is routine in the art and . . . an assay for detecting the catalytic activity of the protein." *Id.* Under the "Analysis" section of Example 14, the requirements of 95% identity to SEQ ID NO:3 and having catalytic activity "are essential to the operation of the claimed invention." *Id.* The procedures of making and testing sequences having 95% identity to SEQ ID NO:3 are determined to be "conventional." *Id.* Example 14 concludes that

> [t]he single species disclosed is representative of the genus because all members have at least 95% structural identity with the reference compound and because of the presence of an assay which applicant provided for identifying all of the at least 95% identical variants of SEQ ID NO:3 which are capable of the specified catalytic activity. One of skill in the art would conclude that applicant was in possession of the necessary common attributes possessed by the members of the genus.

Id. at 54-55.

Applicants' claimed invention, though directed to the nucleotide sequences encoding the proteins having brittle-1 activity, is structured similarly to that of the Example 14 claim. The claimed nucleotide sequences encode proteins having 90% identity to SEQ ID NO:18, with the encoded proteins having brittle-1 activity. Like Example 14, there is not substantial variation in the encoded proteins, because the entire genus must have 90% sequence identity to SEQ ID NO:18 and have brittle-1 activity. Procedures for producing proteins having 90% identity to SEQ ID NO:18 are well-known in the art. For example, alterations in a nucleic acid fragment that result in the production of a chemically equivalent amino acid at a given site, but do not affect the functional properties of the encoded polypeptide, are well known in the art, and such alterations can be obtained by, for example, site directed mutagenesis as described in Sambrook *et al.*, *Molecular Cloning: A Laboratory Manual*; Cold Spring Harbor Laboratory Press: Cold Spring Harbor, 1989 (cited in Applicants' Specification at page 14, lines 9-12). Thus, a codon for the amino acid alanine, a hydrophobic amino acid, may be substituted by a codon encoding another less hydrophobic residue, such as glycine, or a more hydrophobic residue, such as valine, leucine, or isoleucine. Similarly, changes that result in substitution of one negatively charged residue for another, such as aspartic acid for glutamic acid, or one positively charged residue for another, such as lysine for arginine, can also be expected to produce a functionally equivalent product. Nucleotide changes which result in alteration of the N-terminal and C-terminal portions of the polypeptide molecule would also not be expected to alter the activity of the polypeptide. *See, e.g.,* Applicants' Specification, page 7, line 29 – page 8, line 9. Alterations in nucleic acid fragments can also be introduced by error-prone polymerase chain reaction (PCR), a technique that is well known by those skilled in the art. *See, e.g.,* U.S.

Patent Nos. 4,683,195 and 4,800,159. Another technique for obtaining homologous proteins is directed molecular evolution. Unlike protein engineering, in which proteins are improved by making specific changes to them, directed evolution involved mutating genes *in vitro* and screening the resulting proteins for desired activity. Other techniques are well known in the art, but Applicants refrain from providing such information as it would be merely cumulative of the information provided above.

Further, Applicants provided a brittle-1 assay from Shannon *et al.*, Plant Physiol. 117:1235-52 (1998), used to identify the proteins having 90% sequence identity to SEQ ID NO:18 that also have brittle-1 activity. The assay in Shannon *et al.* consists of measuring [^{14}C]Glucose uptake from ADP-Glucose (ADP-Glc) and incorporation into methanol- and water-insoluble products as described on page 1239 and Table V of Shannon *et al.* In short, amyloplasts isolated from endosperm tissue are added to a reaction mixture (200 µl, final volume) containing 100 mM Bicine, pH 8.5, 0.5 M sorbitol, 12.5 mM EDTA, 10 mM GSH, 50 mM potassium acetate, and 4 mM [^{14}C]ADP-Glc plus 60 or 80 µl of amyloplast fraction. Amyloplasts are isolated from endosperm tissue of kernels aged between 10 to 14 days past pollination.

It is well-established that an applicant need not disclose that which is known in the art. *In re Buchner*, 929 F.2d 660, 661, 18 USPQ2d 1331, 1332 (Fed. Cir. 1991). Applicants' citation of this reference in the specification should thus be sufficient evidence of written description of the assay.

Applicants thus respectfully submit, in accordance with Example 14 of the Written Description Guidelines, that the claimed invention is supported by sufficient written description in Applicants' Specification.

The Board's recent decision in *Ex parte Kubin*, Appeal 2007-0819 (BPAI May 31, 2007), *available at* http://www.uspto.gov/web/offices/dcom/bpai/prec/fd070819.pdf (last visited Oct. 9, 2007), is distinguishable. In *Kubin*, the claim at issue was directed to "An isolated nucleic acid molecule comprising a polynucleotide encoding a polypeptide at least 80% identical to amino acids 22-221 of SEQ ID NO:2, wherein the polypeptide binds CD48." *Kubin*, Appeal 2007-0819, at 3. The *Kubin* specification "does not disclose <u>any</u> variants in which the nucleotide sequence encoding amino acids 22-221 of SEQ ID NO:2 is varied." *Id.* at 13 (emphasis

added). Further, the Board noted that there was no disclosure of "correlation between function (binding to CD48) and structure responsible for binding to CD48 (other than the entire extracellular domain) such that the skilled artisan would have known what modifications could be made . . . without losing function." *Id.* In light of these facts, the Board concluded that "[p]ossession may not be shown by merely describing how to obtain possession of members of the claimed genus or how to identify their common structural features." *Id.* at 16 (citing *Univ. of Rochester v. GD Searle & Co.*, 358 F.3d 916, 927, 69 USPQ2d 1886, 1895 (Fed. Cir. 2004)). Of particular concern was Appellants failure to "describe[ ] what domains of [SEQ ID NO:2] are correlated with the required binding to CD48, and thus [Appellants] have not described which . . . amino acids can be varied and still maintain binding." *Id.*

Applicants' Specification, however, provides sufficient guidance as to what amino acids could be modified without affecting brittle-1 activity. While the Examiner has focused on lack of disclosure of sequences having 90% plus identity to SEQ ID NO:18, Figure 1 of Applicants' Specification provides a sequence comparison between SEQ ID NO:18 and a known brittle-1 protein (SEQ ID NO:21) that has only 57.3% identity to the claimed sequence, which provides a clear picture of regions of brittle-1 proteins that have high homology, and are thus likely more susceptible to modification, and regions having low or no homology where more modifications can be made. For example, at the N-termini of these sequences, ten of the first 11 amino acids are identical, with the lone difference being a conservative amino acid substitution of the valine at amino acid seven of SEQ ID NO:21 to an alanine in SEQ ID NO:18. To the skilled artisan, the significant sequence identity at the N-terminus indicates that little or no sequence substitution should be made there, and if made that conservative substitutions would be preferred, in order to maintain brittle-1 activity. Another example of high homology is amino acids 137-219 of SEQ ID NO:21 and amino acids 125-207 of SEQ ID NO:18. Of these 83 amino acids, only six are different. Four of these substitutions are conservative (two glutamines to arginines, an asparagine to threonine, and a phenylalanine to tyrosine), while two are non-conservative (an isoleucine to serine and a threonine to proline). Other regions of high homology, for example amino acids 228-418 of SEQ ID NO:21 and

amino acids 216-404 of SEQ ID NO:18, provide further guidance as to where and what type of substitution could be made.

By contrast, the C-termini of these proteins are significantly different. After amino acid 404 of SEQ ID NO:18 and amino acid 418 of SEQ ID NO:21, not only does SEQ ID NO:18 contain 11 additional amino acids compared to SEQ ID NO:21, but there is also very little sequence homology between the two sequences. Thus, the skilled artisan could expect that amino acid substitutions, deletions, and/or additions in this region would have little effect on brittle-1 activity as compared to, for example, the N-terminal regional. Another region of low sequence homology can be found at amino acids 54-136 of SEQ ID NO:21 and amino acids 61-124 of SEQ ID NO:18. Similar to the C-termini of SEQ ID NOs: 18 and 21, there is a significant difference in amino acid count in this region (83 amino acids for SEQ ID NO:21 and 64 amino acids for SEQ ID NO:18). The skilled artisan could thus conclude that this region of brittle-1 proteins can have significant amino acid substitutions, deletions, and/or substitutions yet still retain brittle-1 activity. Applicants thus submit that the specification provides sufficient guidance as to what regions of SEQ ID NO:18 could be modified and in what way to produce a protein having (1) at least 90% identity to SEQ ID NO:18 and (2) have brittle-1 activity.

Consequently, *Kubin* does not compel a result of lack of written description here and, indeed, should support Applicants' assertion of adequate written description for the claimed invention because Applicants have described a correlation between structure and function for SEQ ID NO:18. *Cf. Kubin*, Appeal 2007-0819, at 17 ("Without a correlation between structure and function, [Appellants'] claim does little more than define the claimed invention by function.").

Similarly, the cases cited by the Examiner in the Non-Final OA in support of the written description rejection do not compel a result of insufficient written description. The Examiner cites *Regents of the University of California v. Eli Lilly & Co.*, 119 F.3d 1559, 43 USPQ2d 1398 (Fed. Cir. 1997), for the principle that "[t]he name cDNA is not itself a written description of that DNA; it conveys no distinguishing information concerning its identity." Non-Final OA, at 6 (quoting *Eli Lilly*, 119 F.3d at 1567, 43 USPQ2d at 1405). In *Eli Lilly*, the patentee described one mammalian insulin cDNA (and thus one vertebrate insulin cDNA), rat insulin cDNA.

Eli Lilly, 119 F.2d at 1568, 43 USPQ2d at 1405. One generic claim at issue in *Eli Lilly* covered all mammalian insulin cDNAs, with no limitation as to identity to the disclosed rat sequence. *Id.* at 1563, 1401. The Federal Circuit thus concluded, as quoted by the Examiner, that

> a generic statement such as 'vertebrate insulin cDNA' or 'mammalian insulin cDNA,' without more, is not an adequate written description of the genus because it does not distinguish the claimed genus from others, except by function. It does not specifically define any of the genes that fall within its definition. It does not define any structural features commonly possessed by members of the genus that distinguish them from others. One skilled in the art therefore cannot as one can do with a fully described genus, visualize or recognize the identity of the members of the genus. A definition by function, as we have previously indicated, does not suffice to define the genus because it is only an indication of what the gene does, rather than what it is.

Non-Final OA, at 6 (quoting *Eli Lilly*, 119 F.3d at 1568, 43 USPQ2d at 1406). Here, Applicants claimed invention is distinguished from other "genera" of brittle-1 proteins by claimed identity to SEQ ID NO:18. All genes covered by the claimed genus are instantly recognizable from those not covered by the claim. The claimed genus is not defined solely by function but, as described above, is defined by the structure of SEQ ID NO:18 and its relationship to known brittle-1 proteins. The Examiner's reliance on *Eli Lilly* is thus misplaced.

The other case that the Examiner cited in the Non-Final OA was *Amgen, Inc. v. Chugai Pharm. Co.*, 927 F.2d 1200,18 USPQ2d 1016 (Fed. Cir. 1991), for the principle that "[i]t is not sufficient to define [a gene] solely by its principal biological property, *e.g.*, encoding human erythropoietin, because an alleged conception having no more specificity than that is simply a wish to know the identity of any material with that biological property." Non-Final OA, at 7 (quoting *Amgen*, 927 F.2d at 1206, 18 USPQ2d at 1021). While Applicants do not question the propriety of this statement, it relates to conception, not written description. Applicants believe that the skilled artisan would not question that Applicants conceived the claim 26 invention. In the statement following the Examiner's quote from *Amgen*, the Federal Circuit held that "when an inventor is unable to envision the detailed constitution of a gene so as to distinguish it from other materials, as well as a method for obtaining it, conception has not been achieved until reduction to practice has occurred, *i.e.*, until

after the gene has been isolated." *Amgen*, 927 F.2d at 1206, 18 USPQ2d at 1021. Under this test, Applicants have (1) detailed the constitution of SEQ ID NO:17 and its variants that encode polypeptides having at least 90% identity to SEQ ID NO:18 so as to distinguish these brittle-1 genes from the prior art, (2) have detailed numerous methods for obtaining the claimed genes (*see, e.g.*, page 15, line 11 – page 16, line 22), and (3) in any event have isolated SEQ ID NO:17 from maize (that is, reduced it to practice). Thus, Applicants conceived the claimed invention.

Other recent Federal Circuit cases support Applicants' position that the claims are supported by sufficient written description. In *Invitrogen Corp. v. Clontech Labs., Inc.*, 429 F.3d 1052, 77 USPQ2d 1161 (Fed. Cir. 2005), the claimed invention related to modified reverse transcriptases (RTs) having DNA polymerase activity and reduced RNase H activity, wherein the RTs were encoded by nucleotide sequences derived from a retrovirus, yeast, Neurospora, Drosophila, primates, or rodents. *Invitrogen*, 429 F.3d at 1072, 77 USPQ2d at 1174. The unmodified RTs from this list of organisms were known, and the specification provided test data for the one disclosed modified RT (that is, the only disclosed sequence actually covered by the claim). *Id.* In affirming the district court's finding of sufficient written description, the Federal Circuit distinguished *Eli Lilly* and *Fiers v. Revel*, 984 F.2d 1164, 25 USPQ2d 1601 (Fed. Cir. 1993), noting that "[i]In those cases, the patent specifications at issue did not identify the sequence (structure) of any embodiment of DNA claimed therein." *Invitrogen*, 429 F.3d at 1073, 77 USPQ2d at 1175-76. Here, Applicants claimed genus is of a similar, and probably smaller, scope as that in *Invitrogen*.[1] Applicants' Specification discloses SEQ ID NO:18 (equivalent to the known RT sequences), and Applicants claim a genus having identity thereto in combination with brittle-1 function. While Applicants did not provide test data, the lack of working examples should not affect the written description analysis. *See Falkner v. Inglis*, 448 F.3d 1357, 1366, 79 USPQ2d 1001, 1007 (Fed. Cir. 2006) (confirming that "examples are not necessary to support the adequacy of a written description . . ." (emphasis in original)).

[1] The scope of the *Invitrogen* genus covers any modification to any RT from any of the claimed organisms, so long as the RT has DNA polymerase activity and reduced RNase H activity.

In *In re Wallach*, 378 F.3d 1330, 71 USPQ2d 1939 (Fed. Cir. 2004), the applicants there disclosed actual possession of a tumor necrosis factor binding protein II ("TBP-II"). *Wallach*, 378 F.3d at 1331, 71 USPQ2d at 1940. From the isolated TBP-II protein, the applicants obtained the N-terminal portion (the first ten amino acids) of the isolated protein. *Id.* The applicants demonstrated that the isolated TBP-II inhibited the cytotoxic effect of tumor necrosis factor. *Id.* From this disclosure, the applicants claimed isolated polynucleotides encoding TBP-II. *Id.* at 1331-32, 1940. In finding lack of written description for the polynucleotide claims, the Federal Circuit first noted that

> the complete amino acid sequence of a protein may put one in possession of the genus of DNA sequences encoding it, and that one of ordinary skill in the art . . . may have therefore been in possession of the entire genus of DNA sequences that can encode the disclosed partial protein sequence, even if individual species within that genus might not have been described or rendered obvious.

Id. at 1333, 1942. The *Wallach* applicants failed this test because, while they may have had actual possession of TBP-II, "possession of the protein says nothing about whether they were in possession of the protein's amino acid sequence." *Id.* at 1334, 1943. Applicants here, however, demonstrated possession of the amino acid sequences covered encoded by the claimed polynucleotides, and, as noted in *Wallach*, Applicants should not be required to "list every possible permutation of the nucleic acid sequences that can encode a particular protein for which the amino acid sequence is disclosed. . . ." *Id.* at 1334, 1942.

As noted in *Capon v. Eshhar*, 418 F.3d 1349, 76 USPQ2d 1078 (Fed. Cir. 2005) "[p]recedent distinguishes among generic inventions that are adequately supported, those that are merely a 'wish' or 'plan,' the words of *Fiers v. Revel*, 984 F.2d at 1171, and those in between, as illustrated by *Noelle v. Lederman*, 355 F.3d [1343, 1350, 69 USPQ2d 1508 (Fed. Cir. 2004)]; the facts of the specific case must be evaluated." *Capon*, 418 F.3d at 1360, 76 USPQ2d at 1086. In *Fiers*, one party in an interference claimed that disclosure of how a skilled artisan could, by reverse transcription, obtain an undisclosed DNA sequence was sufficient to support written description of the count.[2] *Fiers*, 984 F.2d at 1170, 25 USPQ2d at 1605-06. The

[2] The count read: "A DNA which consists essentially of a DNA which codes for a human fibroblast interferon-beta polypeptide." *Fiers*, 984 F.2d at 1166, 25 USPQ2d at 1603.

Board disagreed, and the Federal Circuit affirmed, holding that "[a]n adequate written description of a DNA requires more than a mere statement that it is part of the invention and reference to a potential method for isolating it; what is required is a description of the DNA itself." *Id.* The specification at issue "just represent[ed] a wish, or arguably a plan, for obtaining the DNA." *Id.* at 1171, 1606. Conversely, Applicants' claimed invention cannot be considered a mere wish or plan, because Applicants disclosed the sequence of wheat brittle-1 protein, SEQ ID NO:18, along with the actual nucleotide sequence that encodes the protein, SEQ ID NO:17. Applicants thus provided a description of the DNA itself. In *Noelle*, the patentee claimed human CD40CR antibodies on the basis of a American Type Culture Collection deposit of a hybridoma that secreted the mouse form of the antibody. *Noelle*, 355 F.3d at 1349, 69 USPQ2d at 1514. The patentee failed to disclose any structural elements of the mouse antibody and failed to disclose a fully characterized antigen. *Id.* The Federal Circuit found this lack of disclosure fatal to the patentee's asserted written description sufficiency, holding that no structural elements for the antibody were disclosed in *Noelle* specification. *Id.* at 1349-50, 1514 (noting that the patentee "attempted to define an unknown by its binding affinity to another unknown"). Though not explicitly stated in *Noelle*, the court implied that deposit of the hybridoma was sufficient disclosure of the mouse antibody in accordance with *Enzo Biochem, Inc. v. Gen-Probe Inc.*, 323 F.3d 956, 964, 63 USPQ2d 1609, 1613 (Fed. Cir. 2002). *Noelle*, 355 F.3d at 1349, 69 USPQ2d at 1514. Unlike *Noelle*'s "in between" position on the written description spectrum, Applicants' Specification includes description of brittle-1 structural elements, that is, the actual wheat sequence set forth in SED ID NO:18. Because Applicants' Specification contains structural disclosure beyond that of *Fiers* (only a wish or plan there) and *Noelle* (description of mouse antibody only through deposit of hybridoma producing that antibody), Applicants respectfully submit that their Specification describes the claimed genus of brittle-1-encoding polynucleotides.

In light of the above arguments, Applicants respectfully request withdrawal of the rejections of claims 26 and 30-40 under 35 U.S.C. § 112, first paragraph, written description.

B. Claims 26-29 are Enabled Under 35 U.S.C. § 112, 1st Paragraph.

Claims 26-29 stand rejected under 35 USC 112, first paragraph, because the Applicants' Specification while being enabling for nucleic acids encoding a SEQ ID NO:18 and constructs and vectors comprising them, allegedly does not reasonably provide enablement for nucleic acids encoding a protein with 90% identity to SEQ ID NO:18 and constructs and vectors comprising them. During prosecution, the Examiner asserted that "[t]he instant specification fails to provide guidance for how to make or isolate nucleic acids encoding proteins with 90% identity to SEQ ID NO:18—specific hybridization or PCR conditions, probes or primers are not recited." Non-Final OA, at 3. Further, the Examiner asserted that "[t]he instant specification fails to teach essential regions of the encoded protein." *Id.* at 3-4. The Examiner also stated that

> [t]he instant specification fails to provide guidance for which amino acids of SEQ ID NO:18 can be altered and to which other amino acids, and which amino acids must not be changed, to maintain adenylate translocator activity of the encoded protein. The specification also fails to provide guidance for which amino acids can be deleted and which regions of the protein can tolerate insertions and still produce a functional enzyme.

Id. at 4. The Examiner thus concluded that, because Applicants' Specification allegedly does not describe transformation of plants with a gene encoding a protein having 90% identity to SEQ ID NO:18, "undue trial and error experimentation would be required to screen through the myriad of nucleic acids encompassed by the claims and plants transformed therewith, to identify those with altered starch, if such plants are even obtainable." *Id.* at 5.

Applicants agree with the Examiner that a specification must enable one of ordinary skill in the art to make and use the claimed invention without undue experimentation. Applicants respectfully submit, however, that the Examiner's conclusion of nonenablement of sequences having 90% identity to SEQ ID NO:18 is erroneous because any experimentation needed to practice the present invention would be routine. "[A] patent specification complies with the statute even if a 'reasonable' amount of routine experimentation is required in order to practice a claimed invention, but that such experimentation must not be 'undue.'" *Enzo Biochem, Inc. v. Calgene, Inc.*, 188 F.3d 1362, 1371, 52 USPQ2d 1129, 1135 (Fed.

Cir. 1999). Factors to consider when deciding whether experimentation is undue include: "(1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims." *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988). Applicants address each of the *Wands* factors below.

(1) The quantity of experimentation needed is quite low. As noted above, methods of producing nucleotide sequences are well-known in the art. A method of testing for brittle-1 activity cited in Applicants' Specification is known in the art and is summarized in the Written Description section of this brief.

(2) Applicants' Specification provides sufficient direction for producing nucleotide sequences encoding proteins having 90% identity to SEQ ID NO:18 and a specific assay for brittle-1 activity is provided.

(3) Applicants admit that there are no working examples showing brittle-1 activity in Applicants' Specification. A specification's lack of working examples, however, does not automatically equate to nonenablement of the claimed invention.

> A claim will not be invalidated on section 112 grounds simply because the embodiments of the specification do not contain examples explicitly covering the full scope of the claim language. That is because the patent specification is written for a person of skill in the art, and such a person comes to the patent with the knowledge of what has come before.

LizardTech, Inc. v. Earth Resource Mapping, Inc., 424 F.3d 1336, 1345, 76 USPQ2d 1724, 1733 (Fed. Cir. 2005) (internal citation omitted).

(4) The invention is one of nucleotide sequences encoding proteins having brittle-1 activity. Such an invention requires some experimentation for even routine techniques.

(5) Brittle 1 protein (BT1), the major protein in amyloplast envelope membranes of wild-type maize endosperm, is required for normal levels of starch accumulation in maize kernels. Loss of BT1 in the brittle1 (bt1) mutant results in an 80% reduction in kernel starch. The relation of BT1 to starch accumulation was investigated in two well-characterized maize endosperm suspension-cultured cell lines which were derived from 10 days post pollination (DPP) kernels of inbred A636

and 12-DPP kernels of the waxy mutant in the A636 background. Starch in A636 endosperm cultures accounted for about 1.5% of the fresh weight of cells but BT1 was not detectable in amyloplast membranes or in microsomal membranes isolated from the cultured cells.

In vivo studies of carbohydrate metabolism during development of maize kernels showed that bt1 kernels accumulated more than 13 times as much adenosine 5'-diphosphoglucose (ADP-Glc) as normal kernels. Activity of starch synthase in bt1 endosperm was equal to that in endosperm extracts from normal kernels. The ADP-Glc accumulation in bt1 endosperm cells was not due to a deficiency in starch synthase, and results indicated that AGPase is the predominant enzyme responsible for *in vivo* synthesis of ADP-Glc in bt1 mutant kernels.

(6) This invention is related to the biotechnical arts in a well-known pathway, the transport of ADP-glucose from the cytosol to the plastid, and the skill level of the artisan is very high. *See, e.g., Kubin*, Appeal 2007-0819, at 14 (noting that the level of skill in the molecular biology art is high). The skilled artisan is therefore very familiar with the pathway and well versed in many methods and techniques of, for example, gene manipulation, protein synthesis, and enzyme action.

(7) Claim 26 is directed to a nucleotide sequence encoding a protein having a specified activity. It is unreasonable for Applicants to provide a cookbook recipe of how to practice the invention. Rather, Applicants have depended on the skill and experience of the skilled artisan to implement the invention using nucleotide sequences encoding polypeptides having brittle-1 activity. Applicants expect that the skilled artisan would be aware of successful molecular biology and biochemistry methods and therefore be capable of producing the described sequences and testing these sequences for brittle-1 activity.

(8) The Examiner's concerns about the number of possible sequences having 90% identity to SEQ ID NO:18 are unfounded. *See, e.g.,* Second Final OA, at 4 ("Making all possible single amino acid substitutions in an [sic] 432 amino acid long protein . . . would require making and analyzing 19^{432} (2.6×10^{552}) nucleic acids; these proteins would have 99.8% identity to SEQ ID NO:18."). Indeed, the number of possible claimed sequences should not itself form the basis of an enablement rejection. *See, e.g., Novozymes A/S v. Genencor Int'l, Inc.*, 446 F. Supp. 2d 297,

330 (D. Del. 2006) (noting that, with claims 95% identity to a disclosed sequence, a "large number [of possible sequences] alone is not sufficient to show a lack of enablement . . .").

Outside of factor (3), the *Wands* factors support Applicants assertion that any experimentation required to practice the present claims would be routine. "It is well established that a patent applicant is entitled to claim his invention generically when he describes it sufficiently to meet the [enablement requirement]." *Amgen*, 927 F.2d at 1213, 18 USPQ2d at 1027. In *Amgen*, the court found that a generic claim covering all possible DNA sequences encoding any polypeptide having an amino acid sequence "sufficiently duplicative" of erythropoietin ("EPO") and which causes bone marrow cells to increase production of reticulocytes and red blood cells, and increases hemoglobin synthesis or iron uptake as being nonenabled where the patentee only provided information "of how to make EPO and very few analogs." *Id.* at 1213-14, 1027. As noted in *Novozymes*, however, "[t]he problem in [*Amgen*] was that the claim scope covered <u>any</u> gene that could be used to express proteins of various sizes that had one or more of the biological properties of EPO." *Novozymes*, 446 F. Supp. 2d at 330 (emphasis added). Unlike the patentee in *Amgen*, Applicants are not claiming <u>all</u> nucleotide sequences encoding enzymes having brittle-1 activity but merely those having 90% identity to SEQ ID NO:18. Even the *Amgen* court recognized that the enablement requirement should not be extended beyond reasonableness when it noted that the disclosure at issue there might have been sufficient to enable a claim for EPO analogs similar to those described in that specification. *Amgen*, 927 F.2d at 1213, 18 USPQ2d at 1027 (noting that the patentee's "disclosure might well justify a generic claim encompassing these and similar analogs, but it represents inadequate support for [patentee's] desire to claim all EPO gene analogs").

Applicants' situation is similar to that in *Novozymes*. There, patentee's claim 1 read:

> A variant of a parent *Bacillus stearothermophilus* alpha-amylase, wherein the variant has an amino acid sequence which has at least 95% homology to the parent *Bacillus stearothermophilus* alpha-amylase and comprises a deletion of amino acids 179 an [sic] 180, using SEQ ID NO:3 for numbering, and wherein the variant has alpha-amylase activity.

Novozymes, 446 F. Supp. 2d at 306. *Novozymes* concluded that "requiring at least 95% homology with [the identified sequence] makes the variants sufficiently similar so that the enablement requirement is satisfied. By contrast to *Amgen*, the claim scope [in *Novozymes*] is limited quantitatively to similarity between protein sequences and not just to a requirement for alpha-amylase-like activity." *Novozymes*, 446 F. Supp. 2d at 300. Applicants' current claims are similarly structured. There is a quantitative limit to the similarity between SEQ ID NO:18 and other proteins in the claimed genus and all proteins having 90% identity to SEQ ID NO:18 must have brittle-1 activity. Thus, Applicants' claimed invention should be sufficiently enabled.

Further evidencing enablement of claim 26 is that the novel aspect of the invention is enabled in Applicants' Specification. In a recent Federal Circuit case, the court clarified that "[a]lthough the knowledge of one skilled in the art is indeed relevant [to an enablement determination], the novel aspect of an invention must be enabled in the patent." *Auto. Techs. Int'l, Inc. v. BMW of N. Am., Inc.*, 2007 U.S. App. LEXIS 21271, at *22 (Fed. Cir. Sept. 6, 2007). In the present application, the novel aspect of the invention is the sequence set forth in SEQ ID NO:18 and variants thereof. As SEQ ID NO:18 was present in the sequence listing, which is considered part of the specification as filed, the novel aspect of the invention is enabled in the specification. Whether or not the claimed sequences have brittle-1 activity is irrelevant to the novelty of the claimed sequences; a claim directed solely to "a nucleotide sequence encoding an amino acid sequence having 90% identity to SEQ ID NO:18" would be novel without the brittle-1 activity limitation, which is present for section 112 purposes only. Indeed, brittle-1 activity itself is not novel; as Applicants' Specification notes,

> [b]rittle-1 is one of several corn genes that, when mutated, cause the accumulation of sugars, rather than starch, in developing corn seeds. It has been shown that the brittle-1 gene encodes a plastidic membrane transporter that is involved in the transport of ADP-glucose from the cytosol to the plastid where it is used for starch biosynthesis.

Applicants' Specification, at page 1, lines 12-15 (citation omitted). Therefore, this knowledge can be imputed from those skilled in the art to supplement the present disclosure, as routine experimentation (a brittle-1 assay) provides the determination

of whether a sequence having 90% identity to SEQ ID NO:18 is within the scope of the claim 26 invention. *See Invitrogen*, 429 F.3d at 1070-71, 77 USPQ2d at 1173 ("The scope of enablement . . . is that which is disclosed in the specification plus the scope of what would be known to one of ordinary skill in the art without undue experimentation." (quoting *Nat'l Recovery Techs., Inc. v. Magnetic Separation Sys., Inc.*, 166 F.3d 1190, 1194, 49 USPQ2d 1671, 1674 (Fed. Cir. 1999))).

Kubin also supports Applicants' enablement arguments. As noted above, the *Kubin* Appellants claimed polynucleotides encoding polypeptides having 80% identity to a defined amino acid sequence, which has a defined binding activity. *Kubin*, Appeal 2007-0819, at 3. In Appellants' specification, the Board found that Appellants' specification taught how to make variants of the defined amino acid sequence, how to calculate identity between the defined amino acid sequence and the variants, and how to test the variant for the claimed binding activity. *Id.* at 13. The specification did not disclose, however, which amino acids could be changed and still retain the claimed activity, and it did not disclose any actual variants of the defined amino acid sequence. *Id.* The examiner in *Kubin* rejected the claims as lacking enablement for sequences having identity to the defined amino acid sequence because of the absence of working examples and because changes in defined amino acid sequence might alter the function of the variant as compared to the defined amino acid sequence. *Id.* at 10. The examiner there also noted the unpredictability of the molecular biology art. *Id.* at 13. In finding enablement of the claimed invention, the Board agreed with the examiner that the molecular biology art was unpredictable (*Wands* factor 7), but "the other *Wands* factors weigh[ed] in Appellants' favor, particularly the state of the art and the relative skill of those in the art as evidenced by the prior art teachings and Appellants' Specification." *Id.* at 14 (internal citations and markings omitted). Further, the Board noted that "[t]he amount of experimentation to practice the full scope of the claimed invention might have been extensive, but it would have been routine. The techniques necessary to do so were well known to those skilled in the art." *Id.* (emphasis added). Like the *Kubin* Appellants, Applicants here provided teachings on how to make variants of SEQ ID NO:18 (*see, e.g.,* Applicants' Specification at page 15, line 4 – page 16, line 22), described how to calculate the sequence identities between SEQ ID NO:18 and its

variants (*see, e.g.,* Applicants' Specification at page 8, line 34 – page 9, line 17), and provided the Shannon assay to test for brittle-1 activity. Thus, *Kubin* dictates that Applicants' claims are enabled.

Applicants further note that, if Applicants' claimed invention is limited to only those nucleotide sequences encoding SEQ ID NO:18 as suggested by the Examiner, Applicants' patent rights become essentially useless because the skilled artisan could simply modify one amino acid of SEQ ID NO:18 (the sequence of which is undisputedly disclosed in Applicants' Specification), confirm brittle-1 activity by the Shannon assay (undisputedly referenced in Applicants' Specification), yet be outside the scope of the Applicants' claims even though Applicants' Specification disclosed the complete roadmap to working around the exceptionally narrow claims. In essence, the Examiner's scope of enablement rejection produces the absurd result of Applicants' Specification enabling the skilled artisan to avoid infringement of claims covering only nucleotide sequences encoding SEQ ID NO:18, but the same specification failing to enable the same skilled artisan to produce the same modified amino acid sequence if the claims cover sequences having 90% identity to SEQ ID NO:18.

Applicants also believe that any of the arguments presented in the enablement section should be applicable towards establishing that sufficient written description was present in Applicants' Specification as filed and vice versa. As noted in *LizardTech*, "a recitation of how to make and use the invention across the full breadth of the claim is ordinarily sufficient to demonstrate that the inventor possesses the full scope of the invention, and vice versa." 434 F.3d at 1345, 76 USPQ2d at 1733. That the present specification supports possession (written description) of the genus of polypeptides encompassed by the present claims (see above) further evidences enablement of the present claims. All methods for generating the described polypeptide variants were standard in the art at the time of filing. Likewise, methods for testing for the required activity were described in Applicants' Specification (see above). Thus, the possessed genus is enabled, almost by definition.

In view of the foregoing, Applicants respectfully request withdrawal of the Section 112, 1st paragraph, enablement rejections.

VIII. CONCLUSION

For the reasons set forth above, the Board is respectfully requested to reverse the final rejection of pending Claims 26-29 and indicate allowability of all claims.

Please charge any fee due which is not accounted for to Deposit Account No. 501447 (Potter Anderson & Corroon LLP).

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Dated: February 25, 2008

CLAIMS APPENDIX

26. An isolated polynucleotide comprising:

(a) a nucleotide sequence encoding a polypeptide having brittle-1 activity, wherein the polypeptide has an amino acid sequence of at least 90% sequence identity when compared to SEQ ID NO:18, or

(b) a full-length complement of the nucleotide sequence of (a).

27. The isolated polynucleotide of Claim 26, wherein the polypeptide has a sequence identity of at least 95% when compared to SEQ ID NO:18.

28. A recombinant DNA construct comprising the polynucleotide of Claim 26 operably linked to a regulatory sequence.

29. A vector comprising the polynucleotide of Claim 26.

EVIDENCE APPENDIX

A terminal disclaimer, attached herewith, was filed on December 21, 2005, disclaiming the terminal portion of any patent on this application that would extend beyond the expiration date of 6,660,850. The terminal declaimer was reviewed, accepted, and recorded as noted in the March 8, 2006, Final Office Action.

Also attached is Shannon *et al.*, Plant Physiol. 117:1235-52 (1998), admitted into evidence by the Examiner on February 17, 2006.

RELATED PROCEEDINGS APPENDIX

None

Plant Physiol. (1998) 117: 1235–1252

Brittle-1, an Adenylate Translocator, Facilitates Transfer of Extraplastidial Synthesized ADP-Glucose into Amyloplasts of Maize Endosperms[1]

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Amyloplasts of starchy tissues such as those of maize (*Zea mays* L.) function in the synthesis and accumulation of starch during kernel development. ADP-glucose pyrophosphorylase (AGPase) is known to be located in chloroplasts, and for many years it was generally accepted that AGPase was also localized in amyloplasts of starchy tissues. Recent aqueous fractionation of young maize endosperm led to the conclusion that 95% of the cellular AGPase was extraplastidial, but immunolocalization studies at the electron- and light-microscopic levels supported the conclusion that maize endosperm AGPase was localized in the amyloplasts. We report the results of two nonaqueous procedures that provide evidence that in maize endosperms in the linear phase of starch accumulation, 90% or more of the cellular AGPase is extraplastidial. We also provide evidence that the brittle-1 protein (BT1), an adenylate translocator with a KTGGL motif common to the ADP-glucose-binding site of starch synthases and bacterial glycogen synthases, functions in the transfer of ADP-glucose into the amyloplast stroma. The importance of the BT1 translocator in starch accumulation in maize endosperms is demonstrated by the severely reduced starch content in *bt1* mutant kernels.

Starch is synthesized and accumulates in the amyloplasts of storage tissues (Shannon and Garwood, 1984; Boyer et al., 1989; Smith et al., 1997). The enzymatic reactions catalyzed by AGPases (EC 2.7.7.27), starch synthases (EC 2.4.1.21) (Preiss, 1991), SBEs (EC 2.4.1.18) (Cao and Preiss, 1996; Fisher et al., 1996), and starch-debranching enzymes (James et al., 1995; Rahman et al., 1998) are much better understood than the mechanism involved in the transport of substrates across the amyloplast envelope membranes and the compartmentation of AGPase (Pozueta-Romero et al., 1991; Liu et al., 1992; Okita, 1992; Hannah et al., 1993; Villand and Kleczkowski, 1994; Denyer et al., 1996; Pien and Shannon, 1996; Shannon et al., 1996; Thorbjornsen et al., 1996; Möhlmann et al., 1997). One of the major factors hindering progress is the difficulty of isolating highly purified intact amyloplasts and amyloplast membranes from storage organs because of the presence of a dense starch granule(s) within the fragile envelope membrane (Liu and Shannon, 1981; Echeverria et al., 1985; Gardner et al., 1987; Shannon et al., 1987; Shannon 1989).

We recently developed a rapid yet gentle procedure for the isolation of intact amyloplasts and their envelope membranes from immature maize (*Zea mays* L.) endosperms (Cao et al., 1995) and from maize endosperm suspension cultures (Cao and Shannon, 1996). Immunological characterization indicated that *Bt1* encodes the major 39- to 44-kD polypeptides of the purified amyloplast membranes, BT1. Results from several studies support the possibility that BT1 plays a significant role in starch accumulation in maize endosperm. For example, BT1 is specifically deficient in the amyloplast envelope membranes isolated from *bt1*, a starch-deficient endosperm mutant (Cao et al., 1995).

Shannon et al. (1996) demonstrated that ADP-Glc, the direct substrate for starch synthesis, accumulated in *bt1* mutant endosperms and that AGPase is the predominant enzyme responsible for the synthesis of ADP-Glc in *bt1*. In a preliminary report we showed that amyloplasts from young kernels isolated from *bt1* endosperms were only 25% as active in ADP-Glc uptake and conversion to starch as amyloplasts from normal and mutant maize endosperms (Liu et al., 1992). The amino acid sequence deduced from *Bt1* cDNA (Sullivan et al., 1991) shows high homology with mitochondrial adenylate translocators from some species, and in vitro-synthesized BT1 is targeted to the inner chloroplast membrane (Li et al., 1992).

Giroux and Hannah (1994) reported that the BT2 and SH2 subunits of AGPase from maize endosperms are the same size as the recombinant subunits, and suggested that AGPase in maize endosperm may not be located in amyloplasts. Denyer et al. (1996) recently provided evidence that maize endosperm cells contain two isozymes of AGPase, with more than 95% of the total activity being extra-amyloplastic. All of these data support the sugges-

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Abbreviations: ADH, alcohol dehydrogenase; AGPase, ADP-Glc pyrophosphorylase; APase, alkaline pyrophosphatase; BT1 and BT2, brittle-1 and brittle-2 proteins, respectively; DPP, days postpollination; FSBA, 5′-*p*-fluorosulfonylbenzoyl adenosine; hexose-P, hexose phosphate; 3-PGA, 3-phosphoglyceraldehyde; SBE, soluble starch-branching enzyme; SH2, shrunken-2 protein; SS, soluble starch synthase; SUS, Suc synthase; TCE, tetrachloroethylene; UGPase, UDP-Glc pyrophosphorylase.